

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 September 2000 (14.09.00)	
International application No. PCT/BG00/00003	Applicant's or agent's file reference PETKANTCHIN
International filing date (day/month/year) 24 January 2000 (24.01.00)	Priority date (day/month/year) 01 February 1999 (01.02.99)
Applicant PETKANTCHIN, Lubomir Todorov	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

14 July 2000 (14.07.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer Nestor Santesso</p> <p>Telephone No.: (41-22) 338.83.38</p>
--	---

PCT INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
ROYAUME-UNI

Date of mailing (day/month/year) 04 July 2000 (04.07.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference LPB/P32039WO	
International application No. PCT/GB00/00003	International filing date (day/month/year) 06 January 2000 (06.01.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address HARRISON GODDARD FOOTE Belmont House 20 Wood Lane Leeds LS6 2AE United Kingdom	State of Nationality	State of Residence
	Telephone No. +44 113 2258350	
	Facsimile No. +44 113 2304702	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address HARRISON GODDARD FOOTE Tower House Merrion Way Leeds LS2 8PA United Kingdom	State of Nationality	State of Residence
	Telephone No. +44 113 290 1400	
	Facsimile No. +44 113 244 2829	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input checked="" type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Aino Metcalfe Telephone No.: (41-22) 338.83.38
---	---

PCT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 October 2000 (24.10.00)	
International application No. PCT/GB00/00003	Applicant's or agent's file reference LPB/P32039WO
International filing date (day/month/year) 06 January 2000 (06.01.00)	Priority date (day/month/year) 06 January 1999 (06.01.99)
Applicant MARKHAM, Alexander, Fred et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

31 July 2000 (31.07.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer Juan Cruz</p> <p>Telephone No.: (41-22) 338.83.38</p>
--	---



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, C07K 14/47, 16/18, C12Q 1/68, G01N 33/53, A61K 38/17, 48/00, A01K 67/027		A3	(11) International Publication Number: WO 00/40719 (43) International Publication Date: 13 July 2000 (13.07.00)
(21) International Application Number: PCT/GB00/00003 (22) International Filing Date: 6 January 2000 (06.01.00) (30) Priority Data: 9900167.9 6 January 1999 (06.01.99) GB (71) Applicant (for all designated States except US): UNIVERSITY OF LEEDS [GB/GB]; Leeds LS2 9JT (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): MARKHAM, Alexander, Fred [GB/GB]; Molecular Medicine Unit, Clinical Sciences Building, St. James's University Hospital, Leeds LS9 7TF (GB). BONTHRON, David [GB/GB]; Molecular Medicine Unit, Clinical Sciences Building, St. James's University Hospital, Leeds LS9 7TF (GB). (74) Agent: HARRISON GODDARD FOOTE; Belmont House, 20 Wood Lane, Leeds LS6 2AE (GB).			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 26 October 2000 (26.10.00)
(54) Title: TISSUE REPAIR PROTEIN INVOLVED IN OROFACIAL CLEFTING AND USES THEREOF			
(57) Abstract <p>A nucleic acid molecule, fragment or derivative thereof which encodes a tissue repair protein wherein said isolated nucleic acid molecule, fragment or derivative thereof, has the nucleotide sequence of SEQ ID NO:1. The invention also discloses use of the protein, the production of antibodies thereto, reporter gene construct and the use of the nucleic acid, protein, antibodies and products there in diagnosing and treating orofacial clefting, tissue damage and/or for wound healing.</p>			
<pre>87 atggagcggcgagcgagagccggtgtctgcgggacagcccgac M E R R S E S P C L R D S P D 132 cggcgagcggcgagcccgagcgtcaaggggcctccccagtgag R R S G S P D V K G P P P V K 177 gtggcccggtggagcagacccgagcccatgggagcccgagg V A R L E Z O N G S P M G A R G 222 agggcccaagcgcccggtggccagggccgtgggaggtttgatgt R P H G A V A K A V G G L M I 267 cctgtctttgtgtggtggagcagttggagggcctcttgat P V F C V V E O L D G S L E Y 312 gcaacacagagagagaccccgaggtttgtcctggcggaagat D N R E E H A E F V L V R K D 357 gtgcttttttagccagctgtgtggagctgctcctggcctggg V L F S Q L V E T A L L A L G 402 tattctcacagctctgcggcccgcccaaggataatcaagctg Y S H S S A A Q A O G I I K L 447 ggaaggtggagccctctcccccctcagttatgtgacagatgaccc G R H H P L P L S Y V T D A P 492 gacggagacagtgccgagcagctgacagatgtctcatctgtgtg D A T V A D H L Q D V Y H V V 537 acgttgaaatccaatgacaggtgtttcaagttggaagacttg T L K I Q L O S C S K L E D L 582 cctgcggagcagtggaaccatgccaagctccgcaatgccttaag P A Z Q W N H A T V R N A L K 627 gaactgtccaagagatgaaccagagccacattagccaagaatgc E L L K E M N Q S T L A K E C 672 cctctctccagagtgatgtttcatcattgttaatagccat P L S Q S M I S S I V N S T Y 717 tatgccaatgtgtcagcaaccaagtgccagagtttggagatgg Y A N V S A T K C Q E F G R W 762 tataaagtgacagagatgaaagtgaaagagtggaacgagaa Y K K Y K K I K V E R V E E 807 aacctttcagactattgtgtctgtggcagcgtccaatgcat N L S D Y C V L G Q R P M H L 852 ccaaatatgaaccagctggcatccttgggaaacccaagcaacq P N M N Q L A S L G K T N E Q 897 tctcctcacagccaattcaccacagtgactccaatccgaaccaa S P H S Q I N H S T P I R N Q 942 gtgcccgcattcagcccatcagccgctgtcttcttctccc V P A L Q P I H S P G L L S P 987 cagcttagtcacacattggaaggcaaatagccatggcccat Q L S P O L V R Q I A M A H 1032 ctgataaaccaagattgcccgttgcggcctcctggctcacca L I N Q Q I A V S R L L A H Q 1077 catctcagccatcaaccagcagttctgcaacctcaacctc H P O A I N Q O F L N H P P I 1122 cccagagcagtttaagccagagcccaacctctcctgggaagtc P R A V K P E P T N S S V E V 1167 tctccagatctaccagcaagtcagagatgagctgaaggggcc S P D I Y Q Q V R D E L K R A 1212 agtgtgtcccaagctgtcttggcaagtgccattcaaccgaca S V S Q A V F A R V A F N R T 1257 caggagttgtgtcagattcgggtgaaggagagccctgg O G L L S E I L P K F E D P 1302 ccagcctctcagctctcttctagtaaacctgagggccatgcagat T A S O S L L V N L R A M Q N</pre>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LPB/P32039W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 00003	International filing date (day/month/year) 06/01/2000	(Earliest) Priority Date (day/month/year) 06/01/1999

Applicant

UNIVERSITY OF LEEDS et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant.
- ☒ the text has been established by this Authority to read as follows:

TISSUE REPAIR PROTEIN INVOLVED IN OROFACIAL CLEFTING AND USES THEREOF

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☒ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

7

☐ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 14-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 5,6,12 and 26 (as far as in vivo methods are concerned) are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 33,34

Claims 33 and 34 refer to a promoter region of the gene of present application, or effective part thereof, without giving a true technical characterization. Moreover, no such promoter region is defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Articles 5 and 6 PCT).

No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

/GB 00/00003

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 C07K16/18 C12Q1/68 G01N33/53
 A61K38/17 A61K48/00 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q G01N A61K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, STRAND, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 93 16178 A (USA, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 19 August 1993 (1993-08-19) EST01864 abstract page 58; table 6 SEQ ID NO: 823 page 242 page 496 -page 497; claims 1-5,10-12,15-20 --- -/--</p>	7,22



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 July 2000

Date of mailing of the international search report

10/08/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Fuchs, U

INTERNATIONAL SEARCH REPORT

International Application No.

/GB 00/00003

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAARTINEN, V. ET AL.: "Abnormal lung development and cleft palate in mice lacking TGF-beta3 indicates defects of epithelial-mesenchymal interaction" NATURE GENETICS, vol. 11, no. 4, December 1995 (1995-12), pages 415-421, XP000864758 cited in the application abstract page 415, column 1, line 1 -column 2, line 7 page 420, column 1, line 21 - line 41 ---	27-29
P,X	KIKUNO, R. ET AL.: "Prediction of the Coding Sequences of Unidentified Human Genes. XIV. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in vitro" DNA RESEARCH, vol. 6, no. 3, 30 June 1999 (1999-06-30), pages 197-205, XP002142997 SEQ ID NO: KIAA1034 abstract page 197, column 1, line 15 -column 2, line 10 page 198; figure 1 page 199; table 1 page 200, column 1, line 2 - line 9 page 200; table 2.1 page 202; table 3 page 202 -page 203; figure 2 page 204, column 1, line 41 -column 2, line 2 ---	1-4,7, 19,20, 22,36,37
A	BREWER, C. ET AL.: "A Chromosomal Deletion Map of Human Malformations" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 63, no. 4, October 1998 (1998-10), pages 1153-1159, XP000864763 abstract page 1156; table 1 ---	1-32, 35-37
A	COLLINS, A. ET AL.: "A metric map of humans: 23,500 loci in 850 bands" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 25, 10 December 1996 (1996-12-10), pages 14771-14775, XP002142998 cited in the application the whole document --- -/--	1-32, 35-37

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/00003

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DIB, C. ET AL.: "A comprehensive genetic map of the human genome based on 5,264 microsatellites"</p> <p>NATURE, vol. 380, no. 6570, 14 March 1996 (1996-03-14), pages 152-154, XP002095715 cited in the application the whole document</p> <p>-----</p>	<p>1-32, 35-37</p>

INTERNATIONAL SEARCH REPORT

ation on patent family members

International Application No

PCT/GB 00/00003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9316178 A	19-08-1993	AU 2240492 A	25-01-1993
		AU 3665893 A	03-09-1993
		EP 0593580 A	27-04-1994
		WO 9300353 A	07-01-1993
<hr/>			

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference LPB/P32039WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/00003	International filing date (day/month/year) 06/01/2000	Priority date (day/month/year) 06/01/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant UNIVERSITY OF LEEDS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 31/07/2000	Date of completion of this report 11.05.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Zellner, E Telephone No. +49 89 2399 8427 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00003

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-24 as originally filed

Claims, No.:

1-23 as received on 15/02/2001 with letter of 15/02/2001

Drawings, sheets:

1/14-14/14 as originally filed

Sequence listing part of the description, pages:

1-26, filed with the letter of 28.02.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00003

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 33 and 34.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00003

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 33 and 34.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,3,8,10-12,14,15-17,20
	No:	Claims	13, 21, 22, 23
Inventive step (IS)	Yes:	Claims	1,2,3,8,10-12,14,15-17,20
	No:	Claims	4,5,6,7,9
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00003

Reference is made to the following documents:

D1: KIKUNO, R. ET AL.: 'Prediction of the Coding Sequences of Unidentified Human Genes. XIV. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in vitro' DNA RESEARCH, vol. 6, no. 3, 30 June 1999 (1999-06-30), pages 197-205, XP002142997

D2: KAARTINEN, V. ET AL.: 'Abnormal lung development and cleft palate in mice lacking TGF-beta3 indicates defects of epithelial-mesenchymal interaction' NATURE GENETICS, vol. 11, no. 4, December 1995 (1995-12), pages 415-421, XP000864758 cited in the application

D3: WO 93 16178 A (USA, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 19 August 1993 (1993-08-19)

Item I

In the priority document the specific DNA sequences SEQ ID. NOs: 1-4 are not disclosed. Therefore D1 becomes a relevant document under Article 33 (2) (3) PCT for certain claims.

Item V

1. D1 describes SEQ ID. No: KIAA1034 (page 200, Table 2).
According to the sequence comparisons of the Search Examiner said KIAA034 of D1 is identical with SEQ ID NOs: 1 and 2 and almost identical with SEQ ID. NOs: 3 and 4 (see STRAND results).
Therefore said document is novelty destroying for Claims 21 and 22.
Although no utility is described in D1 the DNA as is novelty destroying for a product claim. The utility is an inherent feature which cannot render a known product novel.
The same applies to claim 13 and 23. The wording "pharmaceutical formulation" and "use as a pharmaceutical" is an unspecific term and includes e.g. DNA plus water which is also not distinguished from the DNA of D1.

2. Claim 4 discloses a delivery vehicle as such. Although it is dependent from Claims 1, 2 or 3, Claim 4 itself is neither a "use" claim or a "product for use claim".

Claim 4 does not provide any special technical features and is regarded as obvious. The nucleic acid known as such from D1 would also be incorporated into a delivery vehicle.

Therefore said claim does not involve an inventive step in view of D1 and the skilled persons knowledge.

The same applies to claim 5.

4. The antibodies of Claims 6, 7 are not directed to a specific use, but to antibodies as such. It is obvious for skilled person to derive antibodies from a protein which can itself be derived from a known nucleic acid sequence (D1).

Therefore Claims 6 and 7 are not allowable under Article 33 (3) PCT.

The same applies to claim 9 since the method for detecting antibodies is not specified.

3. Claims 1, 2, 3, 8, 10-12, 14, 15-17 and 20 appear to be novel and inventive. Said claims refer to the use of nucleic and amino acid sequence encoding a tissue repair protein involved in orofacial clefting or the products for use, a method of producing transgenic mammals and methods for treatment and diagnosis in orofacial clefting.

A genomic clone YAC-CP-1 has been provided (Claim 35) which represents the cloning of this cleft palate gene and crosses the breakpoint of two patients.

Proof that human chromosome 2q32 contains a CPO-causative genetic locus has been provided by the cloning of a gene whose function is disrupted by both breakpoints in these patients and the demonstration of mutations within this gene in cytogenetically normal individuals with CPO.

Via the genomic DNA sequence and the combination of EST database sequences the human cDNA SEQ ID NO:1 was identified and the amino acid sequence SEQ ID NO: 2 was deduced (page 14, paragraph 1). In addition, the corresponding mouse gene SEQ. ID. No 3 was identified.

D2 is the closest prior art document describing cleft palate in mice lacking TGF- β 3. There is no evidence that said β -TGF-3 represents the wound repair protein of the present application. Therefore the problem is to define further genes and

proteins involved in cleft palate suitable for therapy and diagnosis.

Item VIII

1. Claim 3 is objected to under Articles 5 and 6 PCT for the following reason:
The claimed protein itself has not been provided and its function has not been determined. Therefore the proteins encoded by SEQ ID NOs. 2 and 4 have not been sufficiently disclosed (Article 5 PCT). Besides it is noted that in the regional phase an objection under lack of industrial applicability should be expected.
2. For the assessment of the present claims 1,2 and 10-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.